



NATIONAL PBM BULLETIN

August 4, 2015

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

ADVERSE CARDIOVASCULAR THROMBOTIC EVENTS WITH NSAIDS: FDA STRENGTHENS WARNING

I. ISSUE

FDA strengthens the warning that nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with an increased risk of serious and potentially fatal cardiovascular thrombotic events, including myocardial infarction and stroke.

II. BACKGROUND

Since 2005, NSAIDs have carried a *Boxed Warning* as well as *Warnings and Precautions* highlighting the risk of heart attack and stroke in their prescription labels. FDA reviewed new safety information concerning NSAIDs and cardiovascular thrombotic events at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held on February 10-11, 2014. Discussions addressed evidence from the following sources:

- A meta-analysis of randomized clinical trials of cardiovascular and upper gastrointestinal events with non-aspirin NSAIDs, conducted by the Coxib and traditional NSAID Trialists' (CNT) Collaboration of the Clinical Trial Service and Epidemiological Studies Units at Oxford University;
- Observational studies;
- Other scientific publications in the medical literature; and
- The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, which is a large, ongoing randomized safety trial comparing cardiovascular event rates among patients with high cardiovascular risk who are randomized to celecoxib, naproxen, or ibuprofen.

III. DISCUSSION

Based on FDA's review, recommended label changes will reflect the findings of an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke associated with NSAID use. Data from FDA's review indicates that this relative risk:

- varies from 10 percent to 50 percent or more, depending on the drugs and the doses studied.
- may become apparent within days to weeks of initiation.
- may increase with longer duration of use.
- seems dose-related based on observational data, with an increase in cardiovascular thrombotic risk occurring consistently at higher doses.
- appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease, although a higher incidence of cardiovascular thrombotic events occurred in patients with a history of cardiovascular disease or risk factors.
- may be lower for naproxen compared to other NSAIDs as suggested by some observational studies along with the CNT meta-analysis, although these studies were not designed to demonstrate superiority of one NSAID over another with regard to safety as well as having other study limitations. Therefore, based on available data, it remains unclear whether the risk for cardiovascular thrombotic events is similar for all NSAIDs.
- Heart failure findings include:



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- an approximately two-fold increase in hospitalizations for heart failure with use of both COX-2 selective and nonselective NSAIDs according to the CNT meta-analysis; and
- increased risk of myocardial infarction, hospitalization for heart failure, and death in patients with heart failure using NSAIDs according to a Danish National Registry study.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

FDA recommends that health care providers:

- *Prescribe the lowest effective dose for the shortest duration possible to minimize the risk for an adverse cardiovascular event in patients treated with an NSAID.*
- *Recognize that some NSAIDs, including those in OTC products such as ibuprofen and naproxen, can interfere with the antiplatelet action of low dose aspirin used for cardiovascular protection by blocking aspirin's irreversible COX-1 inhibition.*
- *Remain alert for the development of cardiovascular adverse events throughout the patient's entire treatment course, even in the absence of previous cardiovascular symptoms.*
- *Discuss with patients the risk versus benefits of prescription NSAIDs and over-the-counter (OTC) NSAIDs.*
- *Inform patients to seek medical attention immediately if they experience symptoms of heart attack or stroke such as chest pain, shortness of breath or trouble breathing, sudden weakness or numbness in one part or side of the body, or sudden slurred speech.*

Providers should continue to report any adverse reactions with the use of any NSAIDS by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. <http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm> . (Accessed 07/09/2015).

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, rheumatologists, pain specialists, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).